Late-Stage Pharmaceutical R&D and Pricing Policies under Two-Stage Regulation

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Abstract

We present a model combining the two regulatory stages relevant to the approval of a new health technology: the authorisation of its commercialisation and the insurer's decision about whether to reimburse its cost. We show that the degree of uncertainty concerning the true value of the insurer's maximum willingness to pay for a unit increase in effectiveness has a non-monotonic impact on the optimal price of the innovation, the firm's expected profit and the optimal sample size chosen for the clinical trial. A key result is that there exists a range of values of the uncertainty parameter over which a reduction in uncertainty benefits the firm, the insurer and patients. We consider how different policy parameters may be used as incentive mechanisms, and the incentives to invest in R&D for marginal projects such as those targeting rare diseases. The model is calibrated using data on a new treatment for cystic fibrosis.

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1 Introduction

The fast pace of growth of health care expenditure relative to GDP growth that has been experienced by most developed countries, especially prior to the global economic crisis (OECD, 2013), has led regulators to look for innovative solutions to deal with the increasing demands on health care budgets. With a general consensus that technological innovation plays a central role in driving increased costs (Weisbrod, 1991), much effort has been targeted towards the process by which new health technologies are adopted and priced. The aim has been to reduce two types of risk faced by regulators: paying for technologies that are not 'good value for money' and adopting technologies whose effectiveness, once deployed, is lower than the efficacy that was demonstrated in the clinical trials upon whose results the adoption decisions were made (Eichler et al., 2011).

Including an assessment of a new health technology's cost-effectiveness has been a common response to the first risk. However, the precise role played by cost-effectiveness results in determining adoption decisions is less than transparent. Even the National Institute for Health and Care Excellence (NICE) in the UK, probably one of the most open institutions in this respect, does not refer to a single value for the cost-effectiveness threshold, but to a range of between £20,000 and £30,000 per Quality Adjusted Life Year gained (NICE, 2008). Running a high quality, large, Phase III trial is instrumental in mitigating the second risk. However, in recent years, there has been a growing interest in risk-sharing agreements (Pita Barros, 2011; Towse and Garrison, 2010; Cook et al., 2008).

Somewhat surprisingly, as health care insurers have grown more concerned about technology-induced expenditure growth, suppliers of innovations have witnessed a substantial reduction in the number of new drugs approved per billion of US dollars spent on R&D (Scannell et al., 2012; Pammolli et al., 2011) and an increase in the average cost of development of a new drug (DiMasi et al., 2003, 2016). This has inspired investigation into the impact of specific regulatory decisions on the incentives to invest in R&D by the industry, including price regulation (Filson, 2012), cost-effectiveness thresholds (Jena and Philipson, 2008), value-based pricing (Danzon et al., 2015) and risk-sharing agreements (Levaggi et al., 2015). Empirical evidence suggests that tighter regulation presents weaker incentives for the industry to invest in R&D, and delays in the adoption of innovations (Danzon and Epstein, 2008; Golec et al., 2010; Vernon, 2005; Danzon et al., 2005; Kyle, 2007).

The tension between the objective of curbing expenditure on health technologies that are already available in the market and the need to incentivise investment in R&D that will lead to future innovations is known as the trade-off between static and dynamic efficiency. However, equity concerns may also be relevant. For a regulatory framework which does not explicitly account for the size of the population to be treated, incentives to invest in R&D are weaker for technologies targeting comparatively rare diseases ('orphan diseases'). One reason why these are comparatively unattractive areas for R&D investment is that predicted sales revenue is proportional to the size of the population to treat, while R&D expenses are largely independent of it (Acemoglu and Linn, 2004; Dimitri, 2012). Moreover, for rare diseases, meeting the requirements set by authorities regulating market access may be more costly, and require a longer period for experimentation, due to the availability of a smaller population from which to obtain a sam-

ple. Hence, disincentives for research into rare diseases may be found at both commercialisation, and development, stages.

A new drug needs to pass two key regulatory stages if it is to be approved for use by a health care insurer. Firstly, it must be deemed to be safe and efficacious. If these conditions are met, the drug can be used, but it must be fully paid for by the patient. If, as is often the case, the majority of the cost is paid by an (often public) health insurer, that insurer must then decide whether the drug can be reimbursed at a particular price. This price is determined according to rules which vary considerably from country to country. The importance of the cost-effectiveness dimension has been growing in recent years. As a result, Phase III clinical trials, which previously aimed only to assess effectiveness, are often accompanied by an economic evaluation.

This paper presents a unified, Bayesian decision-theoretic framework to investigate late-stage R&D incentives for the pharmaceutical industry in the presence of these two, exogenous, regulatory stages. We model a health technology provider operating within a defined jurisdiction (such as at the country level) and define its optimal sampling and pricing policies in a two stage problem. In the first stage, the provider decides whether to run a Phase III trial and, if it does so, the trial's sample size. In making its decision, the provider knows that, should the regulatory authority which reviews the trial evidence deem the treatment to be effective at a predefined level of statistical significance, the provider may apply for reimbursement by a health care insurer in the second stage. This involves proposing a price for the new product which, when combined with the evidence on effectiveness provided by the trial, determines the incremental cost-effectiveness ratio upon which the health care insurer bases its reimbursement decision.

To the best of our knowledge, our model is the first to present a full analysis of how the 'double hurdle', in the form of the regulatory authority and the health care insurer, affects optimal price, expected profit, the 'go/no go' decision for a Phase III clinical trial, and the trial's sample size. A key result is that the degree of uncertainty surrounding the true value of the insurer's maximum willingness to pay for a unit increase in effectiveness has a non-monotonic impact on the optimal price of the innovation, the firm's optimal expected profit and the optimal sample size chosen for the Phase III clinical trial. We identify three ranges for the uncertainty parameter, in which increases in uncertainty have different effects. In the 'low uncertainty' range, increases in uncertainty result in lower prices, lower expected profits and a smaller trial sample size. In the 'high uncertainty' range, the situation is reversed: greater uncertainty leads to higher prices, higher expected profits and a larger trial sample size. For 'intermediate uncertainty', prices are increasing, expected profits decreasing and sample size decreasing in the degree of uncertainty. This implies that there exists a range of values of the uncertainty parameter – the 'intermediate uncertainty' range – over which a reduction in uncertainty benefits the firm, the insurer and patients. Subsequent analysis considers how the regulatory framework may influence a health technology provider's incentive to invest in projects which are deemed by the provider to be 'marginal', that is, ones for which the expected profit is close to zero, by looking at the incentive to research treatments for rare diseases. In particular, we characterise the minimum size of a population to treat such that the firm is incentivised to invest in the development of a new drug. In an application using published data from trials of a new treatment for cystic fibrosis, defined as a rare disease by the Orphanet register of rare diseases (Orphanet, 2014), we show how parameters and regulatory policies in both periods, such as the level of the Type I error that characterises the

regulatory authority's decision and the uncertainty surrounding the level of the payer's maximum willingness to pay for one effectiveness unit, can affect the incentives to invest.

Section 2 presents a brief summary of the literature. Section 3 presents the model. Sections 3.1 to 3.3 provide a non-technical introduction to the model, and additional technical elements that are required to obtain the main propositions are introduced in Section 3.4. Theoretical results for optimal policies at the regulatory and pricing stages are presented in Section 4. Those wishing to skip the technical material and the formal solution of the optimisation problem may omit Sections 3.4 and 4 and move directly to the application, which is presented in a self-contained manner in Section 5. Section 6 discusses the main results, avenues for future research, and concludes.

2 Background

The work builds on a number of statistical and economic approaches to Phase III trial design, drug approval decisions and research on rare diseases. Kikuchi and Gittins (2009) and Kikuchi et al. (2008) propose a 'Behavioural Bayes' model of sample size determination in a Phase III trial which accounts for the costs and benefits of the trial as well as the deployment of the new treatment. The model is 'behavioural' because, following the ideas of Gittins and Pezeshk (2000), although it maximises total expected net benefit from the perspective of the firm developing the drug, the behaviours of the regulator and users of the drug are not assumed to be optimal. The authors model the level of demand for the new treatment as an increasing function of the point estimate of effectiveness from the trial. Willan (2008) and Willan and Eckermann (2010) present Bayesian models of drug development in which the optimal sample size is chosen to maximise the expected value of sample information, minus the costs of the trial.

Acemoglu and Linn (2004) consider the effect of the potential size of markets on pharmaceutical innovation and entry of new drugs. The authors derive an equilibrium condition for the levels of R&D effort and show that, the greater is the market size, the more profitable it is to supply the drug and so the greater will be the research effort required to gain market-leader position. Magazzini et al. (2013) consider the effects of R&D sunk cost and market size on a pharmaceutical company's decision to enter a clinical trial. They present a two-stage model with a number of firms which can enter one or more therapeutic submarkets and compete for customers. In line with Acemoglu and Linn, the authors predict that, the greater is the market size, the higher is the total R&D investment. With lower success rates and a higher cost per trial, fewer firms enter clinical testing. Further, an increase in sunk R&D expenditures lowers the number of trials and firms. Pennings and Sereno (2011) present a real options model of evaluating pharmaceutical R&D under what they term 'technical' and 'economic' uncertainty. They recognise the risk of failure (for example, due to safety issues) during drug development, but do not model clinical trial design or pricing. Dranove and Meltzer (1994) are concerned with the time for new medical entities to be approved in the US and conclude that, since the 1950s, more important drugs reach the market sooner than less important ones.

These models are important precursors to ours, but none of them explicitly combines the optimal choice of a trial's sample size with a price-setting rule, in the presence of uncertainty

surrounding the health care insurer's maximum willingness to pay for a unit increase in effectiveness.

3 The model

We take the perspective of a Health Technology Provider (HTP) considering whether to commission a Phase III clinical trial to evaluate the efficacy of a new drug. Let μ be the expected value of the incremental effectiveness of the new treatment versus standard in the population (assumed unknown to all agents). For simplicity we assume that the trial is placebo-controlled, an assumption which may be justified when there exists no approved treatment, or when the new treatment is given as an add-on to existing standard treatment. The HTP has a prior distribution on μ, defined by a normal random variable with mean μ_0 and variance σ_0^2.

It is assumed that the n responses observed in the trial are used to calculate the sample mean X, an unbiased and consistent estimator of μ:

$$X \mid \mu \sim \mathcal{N}\left(\mu, \frac{\sigma^2}{n}\right), \tag{1}$$

where σ is assumed known to all agents. We use the convention that upper case denotes a random variable (e.g., at the start of the planning horizon, X is a random variable) and lower case denotes its realisation (e.g., at the end of Stage 0, once the trial has concluded, x denotes the realisation of X).

The HTP knows that, if a clinical trial is commissioned, upon its completion, a Regulatory Authority (RA) in charge of granting access to a market with N patients considers the trial's evidence concerning the drug's incremental effectiveness, together with its standard error. There is no threat of entry which challenges the market size N, and so it is assumed that N is known with certainty by the HTP. We call this stage – establishment of prior, trial commissioning, conduct, reporting and RA assessment – 'Stage 0'.

If RA approval is granted, the HTP tries to have the new drug reimbursed by a Health Care Insurer (HCI) by proposing a price, $p > 0$, for the treatment of a single patient in the market. This stage is called 'Stage 1'. In proposing the price, the HTP does not know the value of the HCI's maximum willingness to pay (WTP) for an additional unit of effectiveness, i.e. the cost-effectiveness threshold. Rather, the uncertainty concerning the HCI's maximum WTP, from the perspective of the HTP, is modelled as a random variable so that, in seeking a higher price for the drug, the HTP faces a trade-off: a higher proposed price offers the potential for higher profits, but it reduces the probability that the drug is reimbursed by the HCI.

The HTP's choice variables may be summarised as follows: 1. the Stage 0 decision concerning whether or not to commission a trial and, if a trial is commissioned, what its sample size, n, should be; 2. in the event that RA approval is granted, the Stage 1 decision of proposing a price to the HCI. The HTP's 'planning horizon', over which optimisation takes place, comprises both Stages 0 and 1.

The optimal Stage 1 pricing policy depends on the estimate of incremental effectiveness that results from the clinical trial, which is a random variable from the perspective of Stage 0. Hence

the problem must be solved recursively. The Stage 1 problem is solved first to yield an optimal pricing policy conditional upon x. Then the Stage 0 problem is solved, using the HTP's beliefs about the realisation of X that will result from the clinical trial, to determine whether or not to commission the trial, as well as its optimal sample size, accounting for the optimal Stage 1 pricing policy.

3.1 The Regulatory Authority

Conditional upon meeting a requirement for a minimum sample size, n_{min}, for the trial, the RA's decision is based upon classical frequentist statistical criteria, so that the new treatment is required to show superiority to placebo at a given one-sided level of statistical significance, α, where α is conventionally taken to be 2.5% (Food and Drug Administration, 1998). Hence approval for the new treatment will be granted if and only if $n \geq n_{\text{min}}$ and the observed value of incremental effectiveness, x, exceeds a critical value, $x_{\text{crit}}(n) > 0$, defined as:

$$x_{\text{crit}}(n) \equiv \frac{z_\alpha \sigma}{\sqrt{n}}, \tag{2}$$

where z_α is the standard normal Z-value corresponding to the one-sided significance level, α. If this condition is not satisfied, the treatment is rejected by the RA and is not taken forward to Stage 1. If the condition is satisfied, the HTP proceeds to Stage 1 and proposes a price to the HCI.

3.2 The Health Care Insurer

The HCI aims to ensure that only innovations that are deemed to be 'good value for money' are reimbursed. It compares x with the price, p, proposed by the HTP, using the incremental cost effectiveness ratio (ICER). We ignore differences in costs which are not directly related to the cost of the drug, implying that the ICER considered by the HCI is $p \,/\, x$. The drug is approved if this proposed ICER is less than, or equal to, the HCI's maximum WTP for an additional unit of effectiveness.

From the perspective of the HTP, the value of the HCI's maximum WTP is uncertain and is modelled using a continuous random variable, W, with cumulative distribution function F_W. We assume that F_W belongs to a location-scale family of random variables, meaning that we can characterise any member in terms of the pair (m, s), where m is the expected value (location) of W and the scale, s, can be considered a measure of its uncertainty, or spread. This assumption is commonly applied in economic models of decision making under risk (Meyer, 1987) and covers a wide class of distributions, including the uniform, normal and logistic. It is sufficiently general to contain members that can be used to approximate uncertainty concerning WTP; it is sufficiently simple to allow for a convenient and easily understandable parameterisation.

3.3 The Health Technology Provider's problem

At the beginning of Stage 0, the HTP must decide whether or not it should enter Phase III clinical testing and, if it does, the optimal sample size for the trial. The cost of performing the trial is assumed to be $I_0 + dn$, where $I_0 > 0$ is the fixed cost of setting up the trial and $d > 0$ is the cost of increasing the sample size by one unit.

Once the trial has taken place and x is known, if RA approval is granted, the HTP's Stage 1 problem is to propose a price, p, to the HCI. We assume that the fixed cost of commercialising the drug, together with the marginal production cost, equal zero. This is plausible if production costs are negligible relative to R&D costs, which is true for most pharmaceuticals (Newhouse, 2004; Barton and Emanuel, 2005). In Section 5 we relax this assumption using a simulation.

The HCI will adopt the new drug with probability $1 - F_W\,(\,p\,/\,x\,; m,\,s\,)$, which may be interpreted as the individual expected demand function, $D_W(\,\cdot\,) = 1 - F_W\,(\,p\,/\,x\,; m,\,s\,)$. If the drug is not approved for reimbursement, the HTP makes zero profits. Define $\boldsymbol{\theta} \equiv (\,N,\,x,\,m,\,s\,)$. If the HCI approves the drug for reimbursement, profits are $N\,p$, implying that the Stage 1 expected profit function is:

$$\Gamma_1(\,p;\,\boldsymbol{\theta}\,) = N\,p\,[\,1 - F_W\,(\,p\,/\,x\,; m,\,s\,)\,]\,. \tag{3}$$

As already noted in Section 3, the HTP's problem is solved recursively. Firstly, it establishes an optimal Stage 1 pricing policy as a function of x taking into account uncertainty concerning maximum WTP. It then uses this policy and its prior on μ to solve the Stage 0 problem, make the 'go/no go' decision for the clinical trial, and decide the trial's optimal sample size. At Stage 0, uncertainty on μ is encoded using a normal prior density with mean μ_0 and standard deviation σ_0, so that the prior predictive distribution for X that is used to compute the expected profit over the two stages is normal with mean μ_0 and standard deviation $\sqrt{\sigma_0^2 + \sigma^2/n}$ (Pratt et al., 1995).

In order to derive the main theoretical results of Section 4, it is necessary to state a number of assumptions concerning the probability distribution F_W. These are dealt with in Section 3.4. The reader wishing to skip these more technical aspects and the formal solution to the model may move directly to the application in Section 5.

3.4 Characterisation of the distribution for WTP

Following the ideas in Meyer (1987), Van den Berg (2007) and Johnson and Myatt (2006), we introduce the following assumptions on the probability distribution for W.

A1 (Location-scale family)

Let T be a random variable with zero mean and finite variance. Assume that the cumulative distribution function of T, F_T, is twice continuously differentiable with probability density function f_T. The cumulative distribution function of the HCI's maximum willingness to pay, F_W, is assumed to belong to a location-scale family of random variables defined by $F_W(w) = F_T(\,(w - m)\,/\,s)$, where m is the location parameter and s the scale parameter.

A2 (Increasing hazard function).

The hazard function of T, $r_T(t) = f_T(t)/(1 - F_T(t))$, is an increasing function for $t \in \mathbb{R}$.

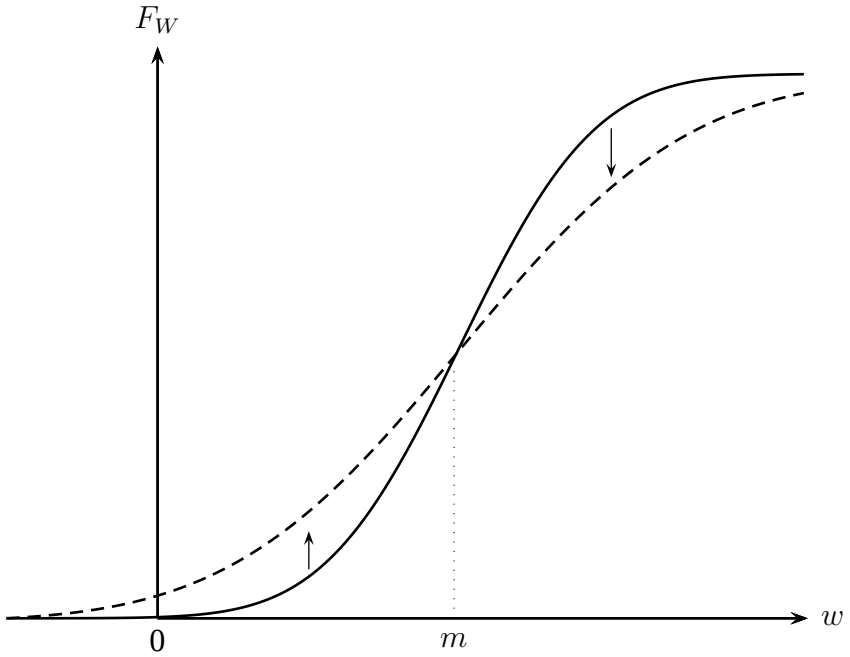


Figure 1: An increase in the uncertainty concerning maximum WTP, s, rotates its cumulative distribution function, F_W, around its location parameter, m.

Assumption **A1** permits us uniquely to define any member of the family describing maximum WTP in terms of the pair (m, s), separating the location and scale properties from the shape of the distribution, which is determined by F_T. It is required to define the existence of an optimal price, as well as to obtain comparative statics results. As shown in Figure 1, the assumption implies that an increase in s rotates F_W around the location parameter m such that F_W increases/decreases according to whether w is less than/greater than m. That is:

$$w \gtreqless m \iff \frac{\partial F_W}{\partial s} \lesseqgtr 0. \tag{4}$$

Intuitively, an increase in s implies that the density is moved from the centre of the distribution to the tails, while ensuring that the distribution functions cross only once, at m. The economic interpretation is that, following an increase in s, the expected demand function, $D_W(\,\cdot\,) = 1 - F_W(\,v\,; m,\, s\,)$, decreases for values of the ICER that are below m and increases for values that are above m.

Assumption **A2** is required to show that the optimal price is unique for every combination of the location and scale parameters and may therefore be considered to be a function of m and s. It may best be interpreted by referring to the concept of increasing duration dependence borrowed from the survival analysis literature: $D_W = 1 - F_W(\,p\,/x\,; m,\, s\,)$ is the probability that the HCI accepts a proposed ICER equal to v. If the HTP increases the ICER by a small amount, Δ, the probability of acceptance, D_W, decreases by approximately $D'_W(v)\,\Delta$. Given acceptance of the technology at v, the conditional probability that the technology is rejected due to this price

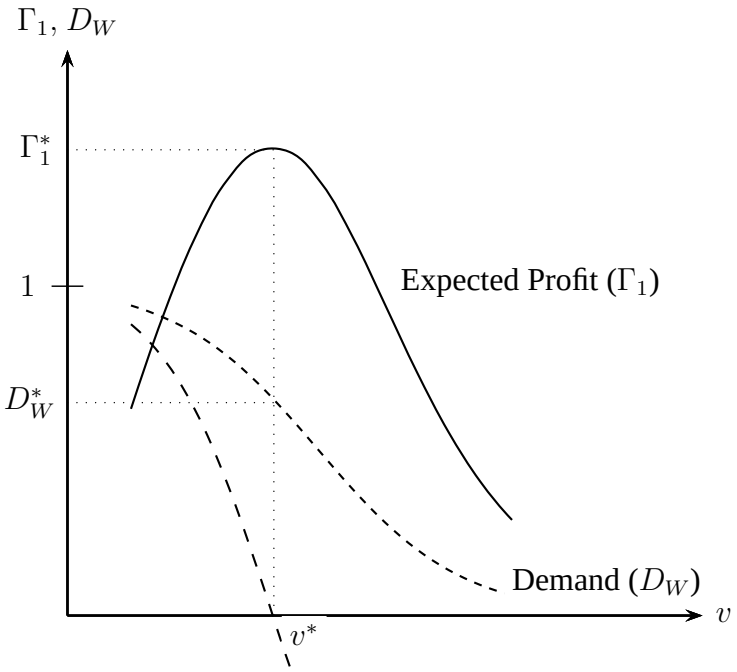


Figure 2: Expected profit function (Eq. (5), continuous line), expected demand function $D_W(\cdot) \equiv 1 - F_W(v; m, s)$ (short dash) and the LHS of Eq. (6) (long dash) showing the optimal choice of the ICER, v^*.

increase is therefore $\Delta(-D'_W(v)/D_W(v))$ and is increasing in w. Thus, we define the marginal risk of rejection as $r_W(v) = -D'_W(v)/D_W(v)$.

4 Optimal Stage 0 and 1 policies

The Stage 1 problem may be thought of as a monopolist's pricing problem, in which marginal cost is equal to zero and there exists a true, fixed, maximum willingness to pay for the new drug. This WTP is unknown to the HTP, who therefore places a probability distribution upon it. The problem is also similar in nature to models such as those of independent private value auctions (Van den Berg, 2007). In this section, we outline the optimal solution for each stage: first, we derive the HTP's optimal Stage 1 pricing policy as a function of the estimate of effectiveness from the trial. Then we solve for the optimal Stage 0 sample size.

4.1 Optimal Stage 1 policy

Define the ICER as $v = p \,/\, x$, where x is known at the start of Stage 1 and p is to be chosen optimally by the HTP. The Stage 1 maximisation problem may be considered from the perspective

of the optimal choice of the ICER, v, by writing Eq. (3) as follows:

$$\Gamma_1^*(\boldsymbol{\theta}) \equiv \max_{v>0} \Big\{ N\,x\,v\,[\,1 - F_W(\,v;\,m,\,s\,)\,] \Big\}. \tag{5}$$

The optimal ICER is the value $v = v^*(m, s)$ which solves the first order necessary condition:

$$1 - F_W(\,v\,;m,\,s\,) - v f_W(\,v\,;m,\,s\,) = 0, \tag{6}$$

or, equivalently,

$$v = \frac{1}{r_W(v\,;m,\,s\,)}. \tag{7}$$

By Assumption **A1**, an optimal solution to the maximisation problem in Eq. (5) exists and satisfies Eq. (6) because the profit function $\Gamma_1(\,v;\,\boldsymbol{\theta}\,)$ is a differentiable function of the ICER, v, on the interval $(0, \infty)$ and the term $v[\,1 - F_W(\cdot)\,]$ in Eq. (5) tends to zero as v tends to infinity, owing to the assumption that T has a finite mean (Van den Berg, 2007). Assumption **A2** implies that $1\,/\,r_W(\,v\,;m,\,s\,)$ is decreasing in v, so that the solution $v^*(m, s)$ of Eq. (7) must be unique.

Figure 2 plots the expected profit function, Γ_1, the expected demand function (short dash), and the LHS of Eq. (6) (long dash) and shows the determination of the optimal ICER, v^*. Note that, according to Assumption **A1**, an increase in s rotates F_W clockwise (Figure 1) and the expected demand function counter-clockwise (Figure 2), both around m. The change in the slope of the expected demand function following an increase in s affects v^* through Eq. (6).

As is clear from comparison of Eqs. (5) and (6), N and x affect the level of optimal profits, but not the optimal choice of the ICER. This provides two simple, but important, expressions for optimal price and profits in terms of the optimal ICER, v^*, which are required to solve the Stage 0 problem. They show that the optimal price is independent of the population size, while being strictly increasing in the effect size, x. This leads to the comparative statics results:

$$p^*(\,x,\,m,\,s\,) = x\,v^*(\,m,\,s\,), \tag{8a}$$

$$\Gamma_1^*(\,\boldsymbol{\theta}\,) = x\,N\,\rho^*(\,m,\,s\,), \tag{8b}$$

$$\text{where } \rho^*(m,s) \equiv v^*(\,m,\,s\,)\,[\,1 - F_W\,(v^*(\,m,\,s\,);m,\,s\,)\,]$$

The following comparative statics expressions for optimal price and profit with respect to N, x and m are formally derived in Appendix A.1:

$$\text{(i)} \quad \frac{\partial \Gamma_1^*}{\partial N} > 0; \quad \text{(ii)} \quad \frac{\partial \Gamma_1^*}{\partial x} > 0; \quad \text{(iii)} \quad \frac{\partial \Gamma_1^*}{\partial m} > 0; \tag{9a}$$

$$\text{(iv)} \quad \frac{\partial p^*}{\partial N} = 0; \quad \text{(v)} \quad \frac{\partial p^*}{\partial x} = v^*(m,s) > 0; \quad \text{(vi)} \quad \frac{\partial p^*}{\partial m} \geq 0. \tag{9b}$$

The results for N and x have been discussed above. For m, the best way to interpret the result is to refer to Figure 2: an increase in m shifts D_W to the right, raising the probability of acceptance at v^*. The HTP may therefore obtain higher expected profits than before, at a higher price, because a marginal increase in v raises expected revenue while the demand, or probability of acceptance, remains above D_W^*.

We next consider results for the response of optimal profit and price to changes in the scale parameter, s, highlighting their importance for this work by stating them as propositions. Both Assumptions **A1** and **A2** are needed in the proofs.

Proposition 1 (**Effect of uncertainty surrounding the HCI's maximum willingness to pay on Stage 1 optimal expected profit).** *Optimal Stage 1 profit is a U-shaped function of the uncertainty, s, surrounding the HCI's maximum willingness to pay for one unit of effectiveness. The function has a global minimum at $\hat{s} = m\, r_T(0)$. Moreover, the optimal ICER proposed by the HTP will be lower/higher than m according to whether s is lower/higher than $\hat{s}$, that is, $m \lesseqgtr v^*(m,\, s\,) \iff \hat{s} \lesseqgtr s$.*

Proof: See Appendix A.1.

Note that, in Proposition 1, a result for the value of v^* relative to m is stated in terms of the value of s relative to $\hat{s}$. Proposition 2 extends this partial result to a full characterisation of the response of the optimal price (and hence the optimal ICER), p^*, to changes in s. Proposition 2 states a sufficient condition which, by ensuring that $\partial v^*/\partial s$ is a strictly increasing function of s and that $\lim_{s\to 0} v^*(m,s) = m$ may be proved, implies a U-shape also for v^* as a function of s. The proposition requires that an assumption be placed on the Mill's ratio, defined as the reciprocal of the hazard function ($M(t) = 1/r_T(t)$), which holds for common distributions such as the normal and the logistic.

Proposition 2 (**Effect of uncertainty surrounding the HCI's maximum willingness to pay on Stage 1 optimal expected price).** *If the Mill's ratio, M, satisfies $M'' > 0$, then the optimal price is a U-shaped function of the uncertainty surrounding the HCI's maximum WTP for one unit of effectiveness, s, with a global minimum at some $\tilde{s} < \hat{s}$.*

Proof: See Appendix A.1.

The economic intuition for these results is as follows. When the uncertainty surrounding the true value of the HCI's maximum WTP is relatively small ('low uncertainty'), the mass of the distribution of W is concentrated around its expected value. Hence, if s increases, a small reduction in the proposed price keeps the probability of adoption by the HCI comparatively high, while causing just a small reduction in the value of revenues conditional upon adoption. Hence p^* decreases with s. On the other hand, if s is very large ('high uncertainty'), a small reduction in p affects the probability of adoption only marginally. Hence, if s increases, it is optimal to increase p^*, to maximise the reward in the event of adoption taking place.

Concerning the relative size of the intervals defining low, intermediate and high uncertainty, Proposition 1 defines the value of $\hat{s}$ as a function of m and the hazard function for the standardised distribution chosen to model maximum WTP ($\hat{s} = m r_T(0)$). As is shown in Appendix A.1, the position of $\tilde{s}$ relative to $\hat{s}$ may also be defined by making reference to this hazard function, using results from Proposition 2. A numerical computation shows that $\hat{s}/\tilde{s} = 2.935$ for the standard logistic distribution that is chosen for the application of Section 5.

Propositions 1 and 2 have important policy implications, because they imply that, for s sufficiently large ($s > \hat{s}$), reductions in uncertainty surrounding the HCI's maximum WTP for one

unit of effectiveness (e.g. by the HCI being more explicit about the decision process that leads to adoption/rejection decisions) induce the HTP to propose lower prices and accept lower expected profits. When there is low uncertainty ($s < \tilde{s}$), the same policy would lead to the opposite result, that is, higher prices and higher expected profits. Interestingly, for intermediate values of uncertainty ($\tilde{s} < s < \hat{s}$), both parties would benefit from greater transparency, because optimal prices would be reduced and optimal expected profits increased. The reason is that, with less uncertainty, it is optimal for HTPs to propose lower prices, but the increase in the probability of acceptance that this would imply is such that expected profits would be higher. Figure 4(a) of the application shows the three regions of s for which these various effects may be observed.

As the uncertainty surrounding the value of the HCI's maximum willingness to pay decreases towards 0 the expected demand function D_W converges towards a step function that equals one when $v < m$ and zero when $v > m$. In this formal limit case, it is clear that the optimal behaviour of the HTP is to choose a price just at the limit of what the HCI will accept, so that $v^* = m$. This suggests that $\lim_{s\to 0} v^*(m, s) = m$ and, further, that, as $s \to 0$, any change in m is matched by an equal change in v^*.

4.2 Optimal Stage 0 policy

At the start of Stage 0, the HTP is in possession of the following information which allows it to make an optimal 'go/no go' decision for the Phase III clinical trial, and to choose the optimal sample size of the trial if the decision is 'go': 1. it has a prior distribution on expected incremental effectiveness, as described at the start of Section 3; 2. it therefore knows, for any sample size n, the prior predictive distribution for the point estimate of incremental effectiveness, X, that will result from the Phase III trial (see Section 3.3); 3. it has solved the Stage 1 problem, which has established the optimal pricing policy and expected reward as a function of the point estimate, x, that results from the trial (Eqs. (8a) and (8b)).

In this section, we explain how the prior predictive distribution for x and the optimal Stage 1 policy may be used to establish the expected reward at Stage 0 for any choice of sample size n and hence the optimal Stage 0 'go/no go' and sample size decisions.

4.2.1 Optimal sample size determination

From the perspective of the start of Stage 0, define $\Gamma_0(n; \cdot)$ as the expected reward of running a Phase III trial with a sample size n and pricing optimally during Stage 1 according to the policy of Eq. (8a) to give the reward in Eq. (8b). In Stage 0, the estimate of incremental effectiveness that will result from the trial is a random variable, X. Hence so are the optimal prices and rewards, since both are linear functions of the realisation of X (see Eqs. (8a) and (8b)).

The Stage 0 optimal choice of n uses the prior predictive density for X to weight the Stage 1 rewards and calculate the expected total reward for the project as a function of n, conditional upon RA approval. Because, from Eq. (8b), Γ_1^* is linear in x, optimal Stage 0 expected profits,

Γ_0^*, may be written as:[1]

$$\Gamma_0^*(\,\cdot\,) \;\equiv\; \max_n \Big\{ N\,\rho^*(\,m,\,s\,)\mathbb{E}\Big[\,X \,|\, X > x_{\text{crit}}(n)\,\Big]\mathcal{P}(\,X > x_{\text{crit}}(n)\,) - (I_0 + dn)\Big\}, \qquad (10)$$

$$\text{subject to } n \geq n_{\text{min}}.$$

$\mathcal{P}$ is the probability that the realisation of x from the trial exceeds the RA's lower acceptance threshold, $x_{\text{crit}}(n)$. Since the prior predictive distribution for X is normal with mean μ_0 and standard deviation $\sigma_p(n) = \sqrt{\sigma_0^2 + \sigma^2/n}$, it follows that

$$\mathcal{P}(\,X \,>\, x_{\text{crit}}(n)\,) \;=\; 1 \,-\, \Phi\left(\frac{x_{\text{crit}}(n) - \mu_0}{\sigma_p(n)}\right), \qquad (11)$$

where Φ denotes the CDF of the standard normal distribution.

Changing the sample size, n, has two effects on expected rewards: firstly, increasing n reduces the standard deviation of the predictive distribution, σ_p; secondly, increasing n lowers the acceptance threshold, x_{crit}. As a result, changes in n change both the conditional expected value of X and the conditional probability, $\mathcal{P}$, in Eq. (10).

For an interior solution, $n^* > n_{\text{min}}$ and $\partial\Gamma_0(\cdot)/\partial n = 0$, implying that the following condition holds:

$$\frac{N\,\rho^*(\,m,\,s\,)\mathbb{E}[\,X \,|\, X > x_{\text{crit}}(n)\,]\mathcal{P}(\,X \,>\, x_{\text{crit}}(n)\,)}{n}\Big(e_{\mathbb{E}[\cdot],n} + e_{\mathcal{P}(\cdot),n}\Big) = d. \qquad (12)$$

The left hand side of this expression is the marginal benefit (MB) of sampling at Stage 0, accounting for the optimal pricing policy and optimal expected reward at Stage 1. The right hand side is the marginal cost (MC). The marginal benefit expression is best interpreted by breaking it into two parts. The term that is not in parentheses measures the expected Stage 1 reward at the (Stage 0) *study-subject* level; the expected contribution made to profits of one study subject recruited to the trial. The term in parentheses is the elasticity of the Stage 1 expected reward with respect to n (by a standard result for the elasticity of a product, this is equal to the sum of the two elasticities that appear in parentheses). These elasticities capture the two aforementioned effects of n on the conditional expectation and the probability of acceptance, respectively.

The per-study-subject expected reward will be strictly positive because $x_{\text{crit}}(n_{\text{min}})$ can never be less than zero. Hence the sign of the marginal benefit function is determined by the signs and sizes of the two elasticities. Since both $\mathbb{E}[\,X \,|\, X \,>\, x_{\text{crit}}(n)\,] > 0$ and $\mathcal{P}(x > x_{\text{crit}}(n)) > 0$, the sign of each elasticity depends solely on the sign of the partial derivative that each contains. In general, marginal benefit may be an increasing, or decreasing, function of n. There will exist a unique optimal value of $n^* > n_{\text{min}}$ if there is a single point where Eq. (12) is satisfied and the marginal benefit function is falling. This situation is illustrated in Figure 3.

[1] This is because expected revenue at Stage 0 is $\int_{x_{\text{crit}}(n)}^{\infty} x f_X\, N\,\rho^*(\,m,\,s\,)\,\mathrm{d}x$, where f_X is the pdf of the prior predictive distribution. Eq. (10) follows because $N\,\rho^*(\,m,\,s\,)$ is a constant and $\int_{x_{\text{crit}}(n)}^{\infty} f_X\, x\,\mathrm{d}x \;=\; \mathbb{E}\Big[\,X \,|\, X \,>\, x_{\text{crit}}(n)\,\Big]\mathcal{P}(\,X > x_{\text{crit}}(n)\,)$.

Although a full characterisation of the Stage 0 optimality condition is hard to obtain because of the aforementioned effects of changes in n, it is possible to state the main Stage 0 result, which concerns the comparative statics results for Stage 0 expected profits and optimal sample size with respect to s for the case of a unique $n^* > n_{\min}$.

Proposition 3 (**Effect of uncertainty surrounding the HCI's maximum willingness to pay on Stage 0 optimal expected profits and optimal sample size).** *(a) If F_W satisfies the assumptions of Section 3 and optimal profit, Γ_0^*, is as defined in Eq.* (10)*, then an increase in uncertainty increases/decreases Stage 0 profits according to whether s is greater than or less than $\hat{s}$ as defined in Proposition 1:*

$$\frac{\partial \Gamma_0^*}{\partial s} \gtreqless 0 \iff s \gtreqless \hat{s}. \tag{13}$$

(b) Suppose F_W satisfies the assumptions of Section 3 and that there exists a unique $n^*(N, m, s) > n_{min}$ which solves Eq. (10)*. Suppose further that the conditions required for applying the implicit function theorem in the computation of $\partial n^*/\partial s$ are fulfilled. Then the optimal sample size is increasing/decreasing in the level of uncertainty according to whether s is greater than or less than $\hat{s}$:*

$$\frac{\partial n^*}{\partial s} \gtreqless 0 \iff s \gtreqless \hat{s}. \tag{14}$$

Proof: See Appendix A.2.

Using the same methods of proof, it is possible to derive comparative static results for optimal profits with respect to N and m under the assumptions of Proposition 3(a) which lead to Eq. (13):

$$\text{(i)} \quad \frac{\partial \Gamma_0^*}{\partial N} > 0; \quad \text{(ii)} \quad \frac{\partial \Gamma_0^*}{\partial m} > 0. \tag{15}$$

Further, under the assumptions of Proposition 3(a) and (b) which lead to Eq. (14), it is possible to derive the comparative static results for optimal sample size with respect to N and m:

$$\text{(i)} \quad \frac{\partial n^*}{\partial N} > 0; \quad \text{(ii)} \quad \frac{\partial n^*}{\partial m} > 0. \tag{16}$$

Two policy implications follow from these results. First, an increase in m, the expected value of maximum WTP, not only increases the expected profit of the project, but also the optimal sample size of the trial. Second, since the optimal sample size, n^*, is an increasing function of the population size, N, it will be optimal to select lower sample sizes for rare diseases and there will exist a lower bound on population size below which no trial will be optimal. This matter is considered next, in the context of the optimal investment decision.

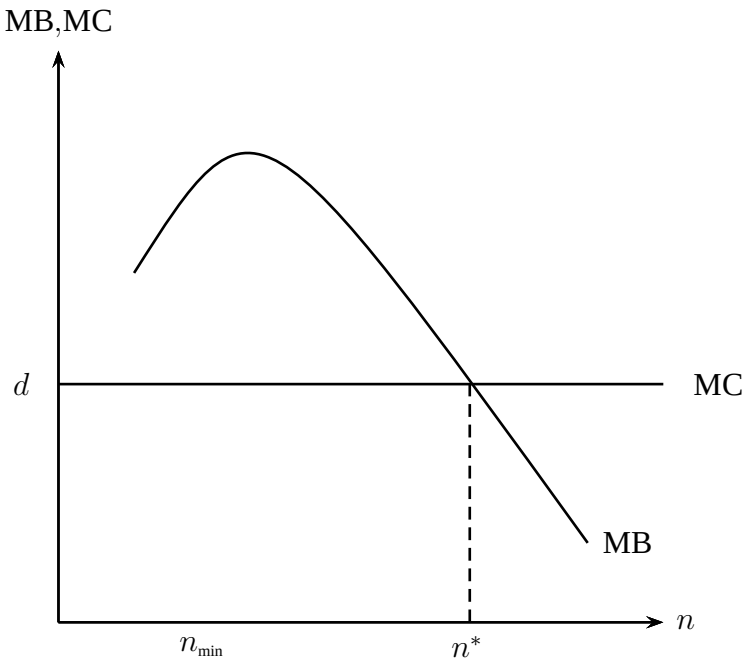


Figure 3: Determination of an interior solution for the optimal sample size at Stage 0 (Eq. (12)).

4.2.2 Optimal investment decision

The dynamic efficiency implications of the regulatory framework that were discussed in Section 1, that is, the incentives for investment in R&D, can be assessed by considering whether or not the HTP chooses to invest in the Phase III trial at the start of Stage 0. Having derived the condition for the optimal sample size, the condition for the optimal investment decision is straightforward. The project will be started if and only if $\Gamma_0^*(\,\cdot\,) > 0$.

Since $\Gamma_0^*(N = 0; \cdot) < 0$ and given Eq. (15(i)), this allows us to define the minimum size of a population to treat, such that the expected profit of investing in the development of a new treatment is positive:

$$N_{\min} = \min\{\, N \parallel \Gamma_0^*(N, \cdot) > 0 \,\}\,. \tag{17}$$

This equation defines a 'marginal project' from the perspective of the market size for the drug and is required for some of the analysis of the incentives to invest in trials for rare diseases that is presented in Section 5.

5 Application

The main theoretical results of Section 4 can be summarised as follows:

- Assuming Stage 1 is reached, which occurs if the RA approves the new drug, both optimal price and optimal expected profit are at first decreasing, and then increasing, in the degree

of uncertainty surrounding the HCI's maximum WTP for one unit of effectiveness. The minimum point of the HTP's optimal price function lies to the left of the minimum point of the Stage 1 optimal expected profit function.

- In Stage 0, both optimal sample size and expected profit over the two stages are first decreasing, and then increasing, in the degree of uncertainty surrounding the HCI's maximum WTP.

The economic intuition for these results has been stated in the paragraphs immediately following Proposition 2. In this section, we provide a calibrated application of the theoretical model, which we believe is important for a number of reasons. Firstly, it illustrates the U-shaped nature of the optimal price, profit and sample size functions that were described in Propositions 1–3. Secondly, it permits us to use published data to provide tentative estimates of the quantitative impact of changes in some key parameters on optimal values. Thirdly, we generalise the model proposed in the theoretical analysis a little. The numerical results obtained in this section are valid for the specific setting under consideration and cannot be easily extended to different applications. However, the quantitative nature of the numerical results is consistent with the theoretical findings of Section 4. Those wishing to apply the framework in their own settings are referred to the code that is released as part of the Online Supplementary Material.

For the model to be operationalised, a functional form for F_W must be specified. We use the logistic distribution, which satisfies all of the assumptions of Section 3.4 and the sufficient condition of Proposition 2. Moreover, it has been used for a recent empirical analysis of how estimates of cost-effectiveness and other variables affect NICE decisions (Dakin et al., 2014), which we refer to in deriving the values of the location and scale parameters.

Throughout Sections 3 and 4, we assumed that there was no cost to produce or commercialise the drug if it were to be approved for reimbursement by the HCI. This allowed us to simplify the proofs of some of the results, in particular concerning the choice of the optimal sample size in Stage 0. In order to enrichen the contribution of our application, we relax this assumption by introducing a parameter representing the production cost per patient treated, $c_p(N) \equiv I_1/N + b$, where $I_1 \geq 0$ is a fixed investment cost and $b \geq 0$ is a constant marginal cost of production. With this assumption, the Stage 1 expected profit function (Eq. (3)) may be written as

$$\Gamma_1(\, p;\, \tilde{\boldsymbol{\theta}}\,) = N(\, p - c_p(N)\,)\,[\,1 - F_W\,(\, p\,/\,x\,;m,\, s\,)\,]\,, \tag{18}$$

where $\tilde{\boldsymbol{\theta}} \equiv (\, N,\, x,\, m,\, s,\, I_1,\, b\,)$. For the parameter values which we choose for the simulation, the qualitative nature of our main results agree with the theoretical results. In particular, we observe a U-shaped optimal Stage 1 profit and optimal price function, provided that $m > c_p(N)/x$ (this is a reasonable condition, since it simply requires that the price that the HTP would choose if HCI's maximum willingness to pay for one effectiveness unit is m for sure, exceeds $c_p(N)$).[2]

[2]The main changes that result from introducing fixed and variable production costs are that the optimal price is no longer independent of N, but decreasing in it, the simple result describing the position of $\hat{s}$ relative to $\tilde{s}$ following Proposition 2 no longer holds and the optimal ICER is no longer independent of x. This, in turn, implies that optimal Stage 1 profit is no longer linear in x, which complicates the theoretical analysis of the optimal Stage 0 policy. Nevertheless, given the parameter values that we choose, the U-shaped behaviour of Γ_0^* and n^* with respect to s that was derived for the case $c_p(N) = 0$ is still observed.

We study the recent NICE health technology appraisal of mannitol dry powder (Bronchitol) for inhalation for treating cystic fibrosis (NICE, 2012b), which is deemed to be a rare disease according to the Orphanet register of rare diseases, with a prevalence of approximately 12.6 per 100,000 in Europe (Orphanet, 2014).

The technology is chosen for a number of reasons. Firstly, the status of cystic fibrosis as a rare disease means that the R&D decision could potentially be considered to be a 'marginal project', that is, one with a market size N that is close to the minimum population size, N_{min}, required for investment to be deemed profitable (refer to Eq. (17)). Secondly, high quality data on the clinical effectiveness, costs and QALYs upon which NICE made its recommendations are available in the NICE report itself and the publications reporting the results of the two key Phase III clinical trials (Bilton et al. (2011) and Aitken et al. (2013)). Thirdly, the control was effectively placebo in both clinical trials, that is, it was the same drug set at a very low, non-therapeutic, dosage. Finally, although the EMA and NICE approved the product for use in 2012 for a sub-group of cystic fibrosis patients (described below), the U.S. FDA denied marketing authorisation in 2013, based on the same clinical trial results, citing concerns over the high level of discontinuation with treatment in the clinical trials and the failure to achieve effects that were statistically significant.

Although the trials reported by and overlapped in calendar time, we assume a hypothetical scenario in which the first trial (Bilton et al., 2011) reported before the second (Aitken et al., 2013). This permits us to use results from the first trial to assign values to the parameters of the model, including the prior mean, μ_0, and variance, σ_0^2 for expected incremental effectiveness, and we take the perspective of a HTP using information from the first trial to decide whether or not to go ahead with the second trial. Full details on the calculations that are used to inform the parameter values are contained in Appendix B.

Table 1 summarises the main parameter values, together with their sources. It should be noted that the application is illustrative and is not intended to be a comment on the efficacy or cost-effectiveness of the technology in question.

5.1 The role of uncertainty

Figure 4(a) shows the U-shaped nature of the optimal ICER (price) and expected Stage 1 profit as functions of the uncertainty parameter, s, and the three regions representing 'low', 'intermediate' and 'high' uncertainty, within which the responses of price and profits to increases in s differ:

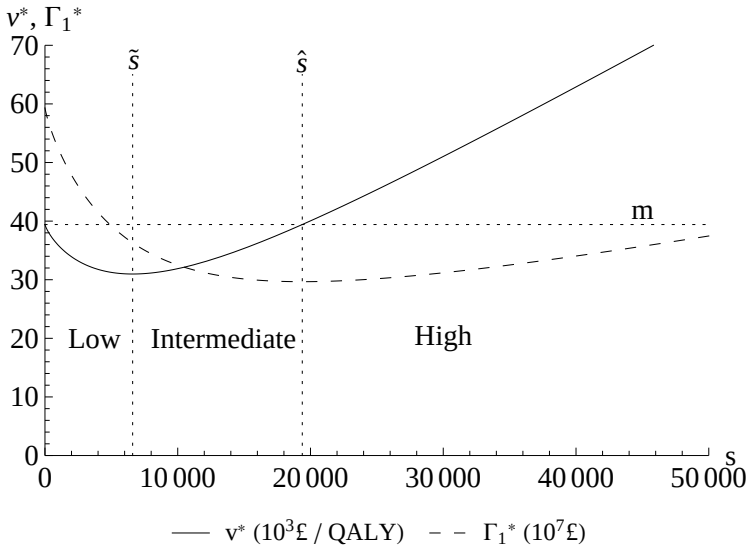
- The 'low uncertainty' range is defined as the region to the left of the minimum point on the optimal ICER function, $\tilde{s}$ = £6,604/QALY. As $s \longrightarrow 0$, the optimal ICER tends to the expected value of maximum WTP for one effectiveness unit (m = £39,417/QALY). In this region, both optimal price and optimal expected Stage 1 profits are decreasing in s.

- The 'high uncertainty' range is defined as the region to the right of $\hat{s}$ = £19,382/QALY, the value of the uncertainty parameter which minimises Γ_1^* and which sets the optimal value of the ICER equal to the expected value of maximum WTP, m, of the HCI (see Proposition 1). In this region, both optimal price and optimal expected Stage 1 profit are increasing in s.

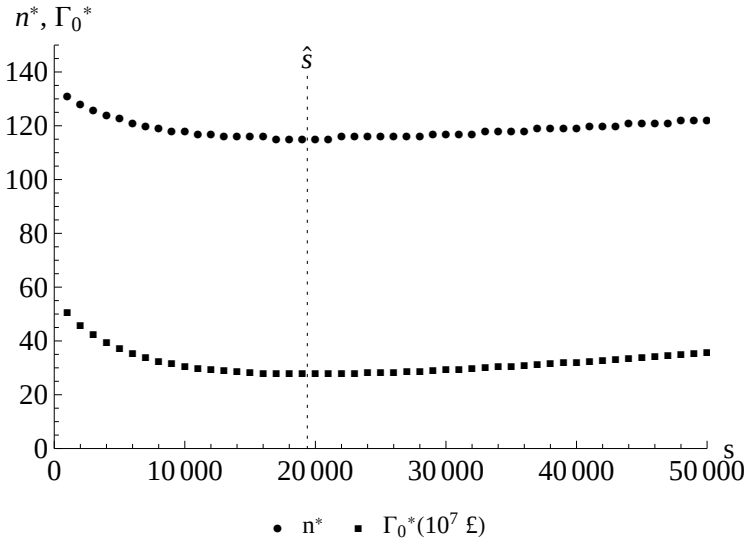
Parameter	Definition	Source	Value
1. μ_0	Expected value of prior beliefs concerning μ	Bilton et al. (2011)	85.0mL
2. σ_0	Standard deviation of prior beliefs concerning μ	Bilton et al. (2011)	16.1mL
3. I_0	Fixed cost of carrying out clinical trial	Assumption	£10,000,000
4. d	Marginal cost of one pairwise allocation	Assumption	£50,000
5. p	Estimated cost of one year's course of mannitol for patient who responds, and adheres to, treatment	NICE (2012a)	£6,041
6.	Estimated cost of placebo	NICE (2012b)	£0
7a. ICER	Incremental cost-effectiveness ratio (using rhDNase)	NICE (2012b)	£47,095/QALY
7b. ICER	Incremental cost-effectiveness ratio (not using rhDNase)	NICE (2012b)	£41,074/QALY
7c. ICER	Incremental cost-effectiveness ratio (not using rhDNase, rapidly declining lung function)	NICE (2012b)*	£29,999/QALY*
8. m	Location parameter of logistic distribution	Dakin et al. (2014)	£39,417/QALY
9. s	Scale parameter of logistic distribution	Dakin et al. (2014)	£11,230/QALY
10. σ	Population standard deviation of incremental effectiveness	Bilton et al. (2011)	190.5mL
11.	Fixed annual prevalence of patients to be treated	NICE (2012a)	10,000
12.	Market exclusivity horizon	EU legislation	10 years
13. N	Size of the population to treat with the new technology	11. and 12.	100,000
14. I_1	Fixed cost of production	Assumption	£10,000,000
15. b	Marginal cost of production	Assumption	£0
16. z_α	Critical value for RA threshold	NICE (2012b)	1.96

Table 1: Parameter values and sources used for the application.

NOTES: *Reported as being under £30,000 per QALY



(a) Optimal ICER and optimal expected Stage 1 profit as functions of the uncertainty parameter, s. The computations were performed assuming that $x = \mu_0$.



(b) Optimal sample size and optimal expected Stage 0 profit as functions of the uncertainty parameter, s.

Figure 4: Optimal Stage 1 ICER and profit and optimal Stage 0 sample size and profit as functions of the uncertainty parameter, s.

- The 'intermediate uncertainty' range is defined as the region lying between $\tilde{s}$ and $\hat{s}$. In this region, optimal price is increasing in s and optimal expected Stage 1 profit is decreasing in s.

Figure 4(b) shows how these non-monotonic Stage 1 responses feed-back to the determination of optimal sample size, n^*, at Stage 0. Both n^* and Γ_0^* are first decreasing, then increasing in s, with the minimum of the two functions occurring at $\hat{s}$.

Although a full welfare analysis is beyond the scope of the present work, the results obtained so far provide some interesting insights. For example, the value of s calibrated using results from the analysis of NICE's decision by Dakin et al. (2014) (£11,230 per QALY) lies between the two threshold values previously reported (£6,604 and £19,382 per QALY). Hence for the specific case under consideration, a reduction of s to any value between these two values would have the following implications: a lower price (Figure 4(a)), a stronger incentive to invest in R&D via expected Stage 0 profits (Figure 4(b)) and more precision on the estimate of the effectiveness via n^* (Figure 4(b)).

Another interesting question is whether, and to what extent, a lack of transparency on the true cost-effectiveness threshold ($s > 0$) can shift rents from the HTP to the HCI. In the formal limit case of $s = 0$ per QALY, assuming $mx > c_p(N)$, the HTP's optimal price in Stage 1 is $p^* = mx$. With the parameter values of our application, and assuming that m is equal to the true value of the HCI's maximum WTP, the optimal sample size for this special case is $n^* = 135$, and the corresponding optimal profit $\Gamma_0^* =$ £575,000,000. In comparison, for the situation where s equals the value calibrated from NICE's actual decisions ($s =$ £11,230 per QALY), $n^* = 117$ and $\Gamma_0^* =$£299,000,000. An interesting extension would be to estimate the Expected Value of Perfect Information about the cost-effectiveness threshold.

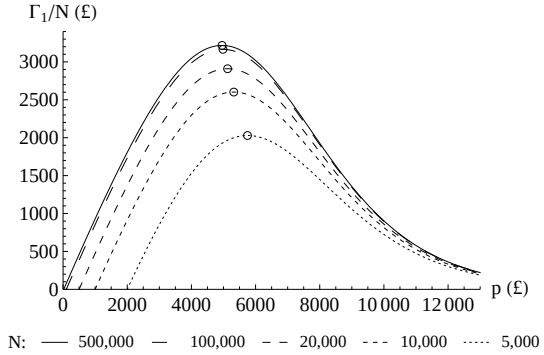
5.2 The role of market size

The results of Section 4 showed that the optimal price setting policy is independent of the size of the population to treat when $c_p(N) = 0$ because the optimal profit per patient would be independent of N. Figure 5(a) shows that this is no longer the case when costs $c_p(N) > 0$ are accounted for in Stage 1. In particular, the optimal price is decreasing in the population size, meaning that, for a comparatively rare disease, it is optimal to propose a higher price. This, in turn, leads to a lower probability of acceptance and lower expected profits per patient.[3]

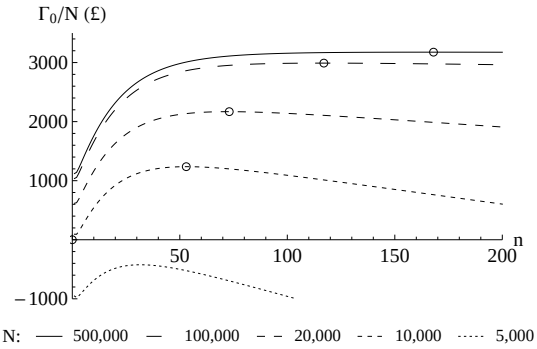
Fixing s at £11,230/QALY, Figure 5(b) shows the Stage 0 profit per patient for different values of the market size as a function of sample size.[4] The figure shows that the optimal sample size increases with the size of the population. In increasing order (that is, as N increases in

[3]The economic intuition for the effect of N on p^* is straightforward. Consider two drugs with very different population sizes, but common fixed costs of production $I_1 > 0$. For both drugs, an increase in p increases expected revenues if the technology is eventually adopted, but also reduces the probability of adoption. Absent fixed investment costs, both terms would be proportional to N and the marginal condition would not be affected. But with $I_1 > 0$, what is left to the firm producing the drug for a less common disease is less. Therefore, the marginal cost due to the reduction in the probability of adoption is less. This leads to a higher value of the optimal price.

[4]Figure 5(b) shows profits per patient, and not total profits, for the sake of clarity. Note that the maximisation problem is unaffected.



(a) Stage 1 expected profit per patient to benefit, (Γ_1/N), as a function of the HTP's proposed Stage 1 price, p, for different values of N. Circles indicate maxima.



(b) Expected profit at Stage 0, (Γ_0/N), as a function of sample size, n, for different values of N. Circles indicate maxima.

Figure 5: Expected profits at the per patient level as a function of price/sample size for various sizes of the market.

Figure 5(b)), the optimal sample sizes for the Stage 0 decision are $n^* = 0$, 53, 73, 117 and 168, respectively. The probability of RA acceptance under the prior, is also strictly increasing in N and may be computed for each specific optimal sample size. Performing this calculation yields values of probability of adoption equal to 0, 0.864, 0.934, 0.983 and 0.995, respectively.

From the policy perspective, the main concern about orphan diseases is the lack of incentives for the firm to undertake R&D projects that could benefit those patients. In Section 4.2.2 we defined N_{min} as the minimum market size such that the HTP would find it profitable to start the project. Figure 5(b) shows that, for the set of parameters used in the calibration, N_{min} is between 5,000 and 10,000.

The analysis presented so far shows that some of the parameters relevant in Stage 1 and which might be, to some extent, under the control of the HCI or the RA may be crucial in providing incentives to invest in R&D. We conclude the discussion of our application with an attempt to investigate quantitatively the role of two parameters characterising Stage 0: α and n_{min}. Figure 6 shows N_{min} as a function of n_{min} for some different values of α, with $5 \leq n_{\text{min}} \leq 80$. As expected, for a given value of n_{min}, N_{min} decreases in the significance level, α, because a stricter policy by the RA (a lower α) requires, other things being equal, larger samples, which pay less in terms of expected profit when the population to treat is small (refer to the per study-subject reward that appeared in the first order necessary condition for the optimal choice of the sample size in Eq. (12)). For a given value of α, N_{min} is non-decreasing in n_{min} because, when the latter is a binding constraint, an increase means that a larger market is required to make non-negative profits. The flat parts of the curves correspond to regions where $n^* > n_{\text{min}}$. Overall, the figure suggests that any policy consideration on the impact of statistical requirements on the incentive to invest in R&D should take both of these parameters into account. In quantitative terms, for the set of parameters used, the impact of increasing α from 2.5% to 20% is to almost halve the value of N_{min} when n_{min} is very small.

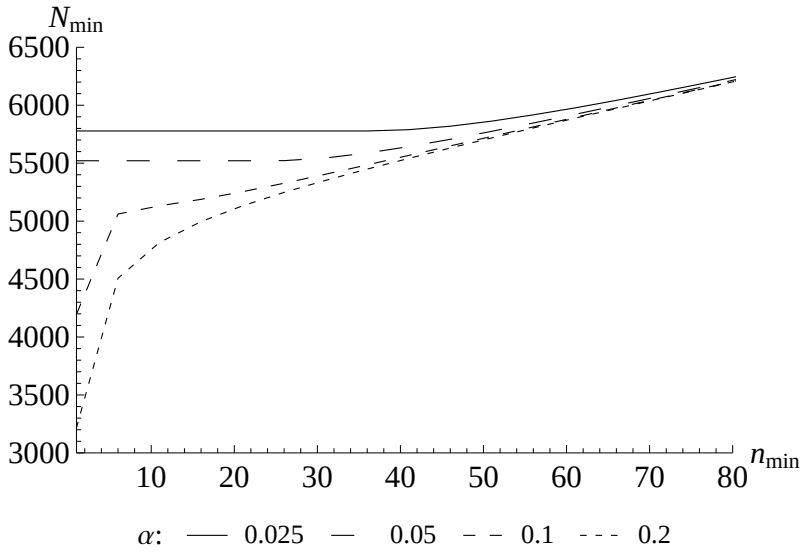


Figure 6: Minimum patient population to benefit ($N_{\min}$) as a function of RA's minimum sample size ($n_{\min}$) for different values of α.

6 Discussion and conclusions

Historically, economic considerations have played a secondary role to the demonstration of safety and efficacy in the drug-approval process. However, the increasing need for regulators to assess the economic implications of their decisions implies that integration between economic and clinical considerations is much greater nowadays. To the best of our knowledge, the two-stage model that we propose is the first to present a full analysis of how regulation of access to the market interacts with the reimbursement decision of a health care insurer, and how exogenous incentives within the regulatory framework either encourage, or discourage, investment in R&D for new pharmaceutical products.

Our main results relate to how the degree of uncertainty surrounding the true value of the health care insurer's maximum willingness to pay for one unit of effectiveness impacts optimal profit, price and sample size. In particular, it is shown that, for reasonable functional forms describing the distribution of beliefs concerning the value of the insurer's willingness to pay, optimal profit, price and sample size are U-shaped functions of the uncertainty parameter. This allows us to identify three regions – 'low uncertainty', 'intermediate uncertainty' and 'high uncertainty' – within which changes in the uncertainty parameter have different qualitative effects. Although a full welfare analysis is beyond the scope of our paper and we cannot characterize the optimal degree of uncertainty either from the societal or the HCI's perspective, the regions provide clear insights on who gains and who loses from changes in the degree of uncertainty. In the 'low uncertainty' region, an increase in uncertainty leads to lower prices, lower expected profits, and smaller sample size. Overall, the policy implication is that, in the 'low uncertainty' region, an increase in uncertainty benefits the insurer via a reduced impact of the new product

on the budget, but it also reduces expected returns for the industry and hence incentives to invest in R&D. Even if development is undertaken, sample sizes of Phase III trials will be smaller. In contrast, in the 'high uncertainty' region, the impact of an increase in uncertainty leads to a higher price, higher expected profit, a larger impact on health budgets, and a larger sample size. A particularly interesting case is that of 'intermediate uncertainty': in this region, by reducing uncertainty, insurers would be better off due to the lower prices and the more precise estimate of effectiveness provided by trials with larger samples; the industry would benefit from larger expected profits; this in turn will benefits patients, especially those with diseases in areas that are of limited interest for the industry, such as orphan diseases, by making the decision to invest in R&D more likely. This final case is of particular interest given the results of the application, which shows that the calibrated value for the uncertainty parameter lies within the intermediate region.

A question that naturally follows from this result is how, in practice, an insurer could change the degree of uncertainty around its maximum WTP for one unit of effectiveness. While many insurers include cost-effectiveness among criteria on which their adoption decisions are based, few of them explicitly state a specific threshold or a range for the maximum value of the ICER. Those that already refer to a specific range could reduce uncertainty by either narrowing the range, or by defining, and making public, rules that affect the adoption decision within that range. For example, a price premium could be explicitly defined as a function of the size of the population to treat, if favouring orphan drugs is an objective, or it could be stated that the upper limit of a range is the relevant cost-effectiveness threshold for drugs targeted to life-threatening conditions.

Concerning incentives that can be provided at the development stage, it has been suggested that this opportunity for regulators might have been under-explored so far (Clarke et al., 2014). Our model provides a framework to investigate this and, in principle, to study the substitutability of incentives at the commercialisation and the development stage. Our application includes a tentative estimate of the impact of a change in the significance level (α) of the statistical test, used by the RA to approve a new drug, on the minimum size of the market that ensures non negative expected profit from an investment in R&D. There is a strong convention within RAs that the type I error rate should be controlled at 5% 2-sided, that is, that the one-sided level, α, should be 0.025. However, the FDA has stressed that this rule is not written in stone and actual FDA decisions for rare diseases confirm this (Sasinowski, 2012). Our results on the consequences of different choices of α are therefore practically relevant.

We conclude with a discussion of a number of limitations of the model and opportunities for future research. It is assumed that there is only one authority which controls access to the market – the RA – and one which decides on reimbursement – the HCI. Although key decisions tend to be concentrated in a limited number of RAs in the real world (e.g. the FDA in the US and the EMA in Europe), this is not the case for insurers. In addition, it is assumed that the regulatory hurdles are set exogenously, and we study the optimal behaviour of the HCI in the presence of these hurdles. A natural next step would be to consider the regulatory process itself as an optimisation problem, and to model the optimal behaviour of both HCI and regulatory agencies.

Regarding reimbursement decisions, our model is based on a 'cost per unit of effectiveness' criterion. However, not all insurers use such an approach. For example, multiple HCIs are active

in the US, and US legislation bans the formal use of cost per QALY for insurance decisions. Both the concept of quality-adjustment of life, and of setting a price on the value of a life (year) are far from uncontroversial. Our model could potentially be extended to allow the sponsor gain to be dependent on decisions from a multitude of RAs and HCIs. Moreover, decisions made in different countries may not be independent, such as when reference pricing mechanisms are adopted. Taking this into account would raise a number of interesting and challenging questions related to strategic interactions and a provider's optimal sequence of reimbursement decisions. Another valuable extension would be the formal modelling of price negotiations at Stage 1.

One could also relax the assumption that the incremental cost of the new technology only depends on the difference between prices. A better technology may, for example, also reduce other health care costs, which would introduce dependency between incremental cost and effectiveness. Methods similar to those used by Kikuchi and Gittins (2009) and Kikuchi et al. (2008) (see Section 2) could be used to model such a relationship.

Although exogenous in our model, the HTP's beliefs about the HCI's maximum WTP could be modelled as endogenous, so that m and s change as the HTP observes decisions made by NICE. In addition, NICE could influence the level of m and s via policy pronouncements, for example by narrowing the declared range of the maximum values of ICER accepted (£20,000 - £30,000 per QALY), or by formally stating how specific characteristics of the technology or the disease (e.g. life threatening conditions) have an impact on the decision.

Although it is acknowledged that the drug discovery and development process extends well beyond the remit of this paper (Pennings and Sereno, 2011), the part of the process that we consider is crucial because of the size of its costs, which are estimated to be around 50% of the total cost of clinical development (Pharmaceutical Research and Manufacturers of America, 2014), and the high probability of failure (estimated to be around 50% in Phase III). Nevertheless, the recursive nature of the solution to the model could permit earlier stages in the drug development process to be added.

Finally, our model has assumed that the RA and HCI refer to a common measure of effectiveness for a single condition. Things get more complicated when RAs and HCIs focus on distinctly different variables: RAs often prefer an objective, 'hard', endpoint, while HCIs may look more at patient-reported quality-of-life. Recently, the EMA has invited HCIs to increase the alignment. In an extension, we could therefore assume the existence of two different, but correlated, response variables, one for each stage of the model. An interesting question would be the degree to which a lack of alignment between RA and HCI objectives could disincentivise drug development. A further extension could consider use of the product for multiple conditions.

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692

A Proofs

A.1 Stage 1

Proofs of comparative static results (Eqs. (9a) and (9b)):

- *Results for* Γ_1^*: Since $v^*(m,s) > 0$ and $0 < F_W < 1$, that $\frac{\partial \Gamma_1^*}{\partial N}$ and $\frac{\partial \Gamma_1^*}{\partial x}$ are positive is immediate from Eq. (8b). By the Envelope Theorem,

$$\frac{\partial \Gamma_1^*}{\partial m} = \frac{\partial \Gamma_1}{\partial m}\Big|_{p=p^*} = Np^* \left(\frac{1}{s}\right) f_T\left(\frac{p^*/x - m}{s}\right) > 0.$$

- *Results for* p^*: Partial differentiation of Eq. (8a) immediately gives $\frac{\partial p^*}{\partial N} = 0$ and $\frac{\partial p^*}{\partial x} = v^*(m,s) > 0$. Since v^* satisfies the first order condition, differentiation of Eq. (7) gives

$$\frac{\partial v^*}{\partial m} r_W(v^*\,;m,\,s\,) + v^*\left(\frac{\partial r_W}{\partial v}(v^*\,;m,\,s\,)\frac{\partial v^*}{\partial m} + \frac{\partial r_W}{\partial m}(v^*\,;m,\,s\,)\right) = 0 \iff$$
$$\frac{\partial v^*}{\partial m} = -\frac{v^*\frac{\partial r_W}{\partial m}(v^*\,;m,\,s\,)}{r_W(v^*\,;m,\,s\,) + v^*\frac{\partial r_W}{\partial v}(v^*\,;m,\,s\,)}.$$

  By Assumption **A2**, $\frac{\partial r_W}{\partial v} \geq 0$. Since $v^* > 0$ and $r_W > 0$ always hold, the denominator of the fraction above is positive and the sign of $\frac{\partial v^*}{\partial m}$ equals the sign of $-\frac{\partial r_W}{\partial m}$. But $\frac{\partial r_W}{\partial m} \leq 0$, so that $\frac{\partial v^*}{\partial m} \geq 0$ and $\frac{\partial p^*}{\partial m} \geq 0$.

□

Proof of Proposition 1:
Let $g(v\,;m,\,s\,) = v r_W(v\,;m,\,s\,)$. Assumption **A2** can be used to show that g is strictly increasing in v:

$$\frac{\partial g(v\,;m,\,s\,)}{\partial v} = r_W(\cdot) + v\,\frac{\partial r_W(\cdot)}{\partial v} \;>\; 0. \tag{19}$$

Note that the hazard function for W is $r_W(w) = r_T\left(\frac{w-m}{s}\right)/s$.[5] As can be seen by rearranging Eq. (6), $g(v^*(m,\,s\,)\,;m,\,s\,) = 1$. Combining this result with Eq. (19) implies that, for any v, $v \lesseqgtr v^*(m,\,s\,)$ if and only if $g(v\,;m,\,s\,) \lesseqgtr 1$. In particular, for $v = m$,

$$m \lesseqgtr v^*(m,\,s\,) \iff m\,r_W(m\,;m,\,s\,) \lesseqgtr 1 \iff m r_T(0)/s \lesseqgtr 1 \iff m r_T(0) \lesseqgtr s.$$

Hence, for any fixed $m > 0$, there exists a value of the scale parameter, $\hat{s} = m r_T(0)$, such that the optimal ICER, $v^*(\cdot)$, is greater than m if and only if $s > \hat{s}$. This observation may be used to characterise the response of Γ_1^* to changes in s. For, by the Envelope Theorem applied to Eq. (8b) and the rotation result for F_W in Eq. (4) (and shown in Figure 1):

$$\frac{\partial \Gamma_1^*}{\partial s} = \frac{\partial \Gamma_1}{\partial s}\Big|_{p=p^*} = -Nxv^*\,\frac{\partial F_W}{\partial s}(v^*;m,\,s\,) \gtreqless 0 \iff v^* \gtreqless m \iff s \gtreqless \hat{s}.$$

[5] The probability density function of W may be written as $f_W(w) = F_T'(\frac{w-m}{s}) = f_T\left(\frac{w-m}{s}\right)/s$. The hazard function for W is therefore: $r_W(w) = \left[f_T\left(\frac{w-m}{s}\right)/s\right] / \left[1 - F_T\left(\frac{w-m}{s}\right)\right] = r_T\left(\frac{w-m}{s}\right)/s$.

□

Proof of Proposition 2:
By making use of the substitution $v = m + st$, we see that solving the first order necessary condition in Eq. (7) for $v > 0$ is equivalent to solving the following transformed problem for $t > -m/s$,

$$(m + st)r_T(t)/s = 1 \iff -m/s = t - 1/r_T(t) \iff \psi(t) = -m/s,$$

where $\psi(t) \equiv t - 1/r_T(t)$. By Assumption **A2**, $\psi(t)$ is strictly increasing. This implies that its inverse ψ^{-1} is well-defined and that the solution to the equation above may be written as $t^* = \psi^{-1}(-m/s)$. The corresponding solution for the original problem is then $v^* = m + s\psi^{-1}(-m/s)$. Fixing m, differentiation with respect to s yields

$$\frac{\partial v^*}{\partial s}(s) = \psi^{-1}(-m/s) + \frac{m/s}{\psi'\left(\psi^{-1}(-m/s)\right)}.$$

Now, since the change of variable $\theta = \psi^{-1}(-m/s) \iff \psi(\theta) = -m/s$ defines a strictly increasing mapping of $s \in (0, \infty)$ on to $\theta \in (-\infty, \psi^{-1}(0))$, $\frac{\partial v^*}{\partial s}(s)$ is strictly increasing if and only if $\theta \mapsto \theta - \frac{\psi(\theta)}{\psi'(\theta)}$ is strictly increasing. Differentiation with respect to θ results in the sufficient condition

$$1 - \frac{\psi'(\theta)^2 - \psi(\theta)\psi''(\theta)}{\psi'(\theta)^2} > 0 \iff \psi(\theta)\psi''(\theta) > 0.$$

Since $\psi(\theta) = \psi(\psi^{-1}(-m/s)) = -m/s < 0$ when $m > 0$, we obtain the sufficient condition $\psi''(\theta) < 0$ for $\theta \in (-\infty, \psi^{-1}(0))$. Because $M(\theta) = \theta - \psi(\theta)$, this is equivalent to $M''(\theta) > 0$.

This concludes the proof that $M'' > 0$ implies that $\frac{\partial v^*}{\partial s}(s)$ is strictly increasing. By combining this result with the result from Proposition 1 that $m \lesseqgtr v^*(m, s) \iff \hat{s} \lesseqgtr s$, it is straightforward to show that $\lim_{s\to 0} v^*(m, s) = m$. This in turn implies that, as s increases, v^* is first strictly decreasing and then strictly increasing, attaining a minimum value at some $\tilde{s}$ which must satisfy $0 < \tilde{s} < \hat{s}$.

□

Position of $\tilde{s}$ relative to $\hat{s}$:
Proposition 1 defines $\hat{s} = mr_T(0)$. There is no closed form solution for the value of $\tilde{s}$. However, from the proof of Proposition 2, it may be shown that $\tilde{s}/m = 1/|\psi(\tilde{\theta})|$, where $\psi(t) = t - 1/r_T(t)$ and $\tilde{\theta} = \text{argmax}_{\theta<0}|\theta|r_T(\theta)$. As a result, the ratio $\hat{s}/\tilde{s}$ may be written as $r_T(0)|\psi(\tilde{\theta})|$ and is entirely determined by the choice of the standardised distribution for the uncertainty concerning the HTP's maximum WTP. Numerical computations show that $\hat{s}/\tilde{s} = 2.935$ for the standard logistic distribution and $\hat{s}/\tilde{s} = 2.946$ for the standard normal distribution.

A.2 Stage 0

Proof of Proposition 3:

Let $\zeta(n) = \mathbb{E}\Big[\, X \,|\, X > x_{\text{crit}}(n) \,\Big] \mathcal{P}(\, X > x_{\text{crit}}(n) \,)$, so that $\Gamma_0 = N\, \rho^*(\, m,\, s\,) \zeta(n) - (I_0 + dn)$. By the Envelope Theorem,

$$\frac{\partial \Gamma_0^*}{\partial s} = \frac{\partial \Gamma_0}{\partial s} \Big|_{n=n^*} = \zeta(n^*)\, N\, \frac{\partial \rho^*(\, m,\, s\,)}{\partial s}. \tag{20}$$

Since $\zeta(n^*)$ is always positive and the sign of $\partial \rho^* / \partial s$ equals the sign of $\partial \Gamma_1^* / \partial s$ (for any fixed, but arbitrary, x), part (a) follows from Proposition 1.

By the implicit function theorem,

$$\frac{\partial n^*}{\partial s} = -\left(\frac{\partial^2 \Gamma_0}{\partial n^2} \right)^{-1} \frac{\partial^2 \Gamma_0}{\partial s \partial n} \Big|_{n=n^*}. \tag{21}$$

By assumption, $\partial^2 \Gamma_0 / \partial n^2 \Big|_{n=n^*} < 0$, and hence the sign of $\partial n^* / \partial s$ equals the sign of

$$\frac{\partial^2 \Gamma_0}{\partial s \partial n} \Big|_{n=n^*} = \frac{\partial^2}{\partial s \partial n} \left(N \rho^* \zeta - (I_0 + dn) \right) \Big|_{n=n^*} = N \frac{\partial \rho^*(m,s)}{\partial s} \frac{\partial \zeta(n^*)}{\partial n}. \tag{22}$$

By definition, n^* solves the first order necessary condition, implying $\partial \zeta(n^*)/\partial n = d/(N \rho^*(m,s)) > 0$. Therefore, the sign of $\partial n^* / \partial s$ equals the sign of $\partial \rho^* / \partial s$, and part (b) follows from Proposition 1.

□

B Sources of parameter values for application

We briefly summarise the results of the two clinical studies considered (Bilton et al. (2011); Aitken et al. (2013)) and the NICE health technology appraisal as it relates to the estimates of cost-effectiveness.

- *The Phase III trials*. Bilton et al. (2011) compared 400 mg of mannitol twice daily with placebo for 324 subjects aged 6 years or over, randomised 3:2 to mannitol and control. The subjects were based in Europe, Australia and New Zealand. At 26 weeks, upon conclusion of the double-blind stage of the study, the authors reported a significant improvement in forced expiratory volume in one second (FEV_1) in subjects receiving mannitol compared with control. Aitken et al. (2013) compared the same dosage of mannitol to placebo for 192 patients aged 6 years or over, again randomised 3:2. Patients were recruited from North America, South America and Europe. The authors reported a statistically significant improvement in FEV_1 for the mannitol group compared with control during the double-blind stage of the study (the first 26 weeks). Both studies included open label periods, running for 26 weeks after the double-blind stage had concluded, intended to collect more data on adverse reactions. The studies also collected data on quality of life, together with other secondary outcome measures.

- *The NICE Health Technology Appraisal's assessment of cost-effectiveness.* Cost-effectiveness was assessed in the manufacturer's submission to NICE using a Markov model comparing treatment with and without mannitol and populated with data from the clinical trials (NICE, 2012a). The NICE technology appraisal calculates ICERs according to subgroups defined according to whether or not patients were using an alternative treatment, rhDNase. The results for the estimated ICER are split by this classification: that for mannitol compared to treatment without mannitol in the rhDNase group is £47,095 per QALY and that for the group not using rhDNase is £41,074. The report summarises the results of various sensitivity analyses which resulted in changes in these estimates and concluded that the high reported ICERs (between £50,000 and £80,000 per QALY) for patients taking rhDNase meant that the treatment could not be recommended for them because it was not cost-effective; the ICER for those not on rhDNase because they were ineligible, intolerant, or because of inadequate response was considered to be above £30,000 per QALY. However, for those in the latter group whose lung function was decreasing rapidly, the ICER was considered to be under £30,000 per QALY (two reported estimates are £27,700 and £30,100 per QALY). The NICE appraisal committee therefore concluded that mannitol could be considered a cost-effective use of NHS resources for this sub-group only.

Bilton et al. (2011) report a statistically significant improvement in FEV_1 compared with placebo ($p < 0.001$) in the first trial. Averaged across the post-randomisation visits, the point estimate of x is reported to be 85.03mL with a 95% confidence interval of (53.5mL,116.6mL) (Bilton et al., 2011, page 1073, section entitled 'Efficacy'). It is therefore assumed that $\mu_0 =$ 85.03mL for the start of the second Phase III trial (Aitken et al., 2013).

The 95% confidence interval reported by Bilton et al. is used to obtain an estimate of σ, the standard deviation of the difference between effects in the treatment and control arms. Assume that the standard deviations in the two trial arms are equal, with a common value, $\sigma/\sqrt{2}$. Then, referencing Table 1 of Bilton et al. (2011), the sample sizes of $n_t = 177$ (number of subjects in treatment arm) and $n_c = 118$ (number of subjects in control arm), an estimate of $\sigma/\sqrt{2}$ may be obtained by rearranging the standard error formula for two independent means when the variance is known:

$$\hat{\sigma}/\sqrt{2} = \text{SE}(X)\left(\sqrt{1/n_t + 1/n_c}\right)^{-1}, \tag{23}$$

where $\text{SE}(X) = (116.6 - 85.03)/1.96 = 16.10$, obtained from the 95% confidence interval. Solving Eq. (23) yields $\hat{\sigma} = \sqrt{2} * 135.5 = 191.63$. Alternatively, we may assume a sample size equivalent to approximately $n = 140$ pairwise allocations and estimate σ directly as $\hat{\sigma} = \text{SE}(X)\sqrt{n} = 16.10 \times \sqrt{140} = 190.5$. The standard deviation for the prior is simply taken to be the standard error, $\sigma_0 = \text{SE}(X) = 16.10$.

The calibration of the values for m and s of the logistic function merit some discussion. The values in units of £/QALY are taken from Dakin et al. (2014), who estimate a number of different regression models for past NICE appraisal decisions and find that the reported ICER was the major factor influencing the probability of acceptance (no other factor, other than the

type of condition, was found to have a statistically significant effect on NICE's decision). For the model with the highest prediction accuracy, Dakin et al. (2014) report that the ICER values corresponding to probabilities of NICE recommendations of 0.25, 0.50 and 0.75 were £51,754, £39,417 and £27,047 per QALY, respectively (Table III, model 4 in Dakin et al. (2014)). The pairs (0.5, 39,417) and (0.75, 51,754), when inserted into the logistic function, give two equations for m and s which can be solved to yield the following estimates: $m =$ £39,417/QALY and $s =$ £11,230/QALY. Now, the unit of the incremental efficacy x is not measured in QALYs, but as FEV1 mL. Hence, when performing computations within the model, it is first necessary to convert incremental efficacy into the corresponding number of QALYs. Calibration gives a conversion factor of 0.0018 QALY/mL.

We assume 10,000 patients treated per year, and a time horizon of 10 years, which is the length of the exclusivity period allowed in the European Union for rare diseases. This implies $N =$ 100,000.

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